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14. ABSTRACT
At the completion of one year, there is empirical evidence that the Parkinson 's disease (PD) ANAM battery is sensitive to neurocognitive change independently identified by traditional neurocognitive testing. Individuals exhibiting mild neurocognitive impairment demonstrated poorer cognitive efficiency on nine ANAM tasks compared with both normal controls and cognitively-intact PD patients. Moreover, the latter two groups did not differ from one another on ANAM performance. The WICE, a comprehensive index of cognitive efficiency weighted so that each of eight ANAM tasks contributed equally, demonstrated that the battery as a whole is sensitive to cognitive impairment subsequent to PD. Age-related differences in ANAM performance were identified by the present study. It was also noted that significantly more female PD patients exhibited cognitive decline than men even though the full PD sample had more of the latter.

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that affects a significant number of individuals in the middle and late stages of life. Over one million Americans are affected by this disorder, and approximately 50,000 individuals are diagnosed with the disease each year. By virtue of the underlying pathology, the degeneration of dopaminergic nigral neurons, PD has relevance for issues facing the military for force health protection [1]. This study was proposed as an initial investigation into the use of an automated computerized battery to assess changes in mood, cognition, and motor control associated with PD. Our initial objective was to demonstrate the feasibility of using selected tests from the Automated Neuropsychological Assessment Metrics (ANAM) test system [2] to assess these areas of neurological functioning in a time- and cost-efficient manner. The secondary objective was to evaluate the general feasibility of using ANAM with PD patients. Outcomes from this initial phase were intended to guide future studies based on the use of ANAM as a tool for monitoring disease progression and medication effects in PD. Future studies might also correlate ANAM test performance with findings from functional imaging studies.

PD affects approximately 1% of the population over age 60. It is the second-most common neurodegenerative disease in adults, next to Alzheimer's disease. PD is one of the more frequently occurring neurodegenerative diseases in the middle to later years of life [3]. Approximately 40% of PD patients develop the disease between ages 50 to 60. In addition, the American Parkinson's disease Association has reported that "early-onset" PD is on the rise and that an estimated 10% of recently diagnosed patients are under the age 40[American Parkinson Disease Association, 1995 in the text I have]. A cognitive impairment rate of 19% of a group of patients with early-onset PD has been reported [4]. Increasing age was also found increased the risk of PD-associated cognitive impairment. Thus, while motor symptoms have been recognized since the disease was first described by James Parkinson in 1817 [6], it is now clear that impaired cognition, ranging from mild to frank dementia, is an important aspect of PD[7-9]. A variety of psychiatric alterations including depression, anxiety, and psychosis may also manifest as the disease progresses.

Assessment and monitoring of cognition is important in PD; however, the integration of neurocognitive assessment into standard model of PD care has been difficult. For example, the Mini Mental Status Exam (MMSE) [10] is frequently given in neurology clinics to assess cognitive status. Although the MMSE is brief and produces a summary score that facilitates tracking, it has two major disadvantages. First, because of its brevity, it does not adequately assess different cognitive domains or patterns of impairment within domains. Second, it is more sensitive to cortical dementia than to cognitive changes related to subcortical pathology seen with PD [11]. Hence, there is a clear need for a brief cognitive assessment measure for these patients. Such a tool must be sensitive to cognitive changes, but does not need to be as comprehensive or extended as a full neuropsychological examination. It should be significantly sensitive to PD-related impairment to identify patients might benefit from more extensive neurocognitive evaluation. In addition, this cognitive assessment tool should be repeatable and sensitive to changes that may occur secondary to disease progression and treatment interventions, both medical and surgical. Such a brief repeatable cognitive battery could also be used when studying new medications for the treatment of PD.

Although the precise incidence of PD-associated cognitive impairment has been difficult to assess due to confounding factors, estimates have ranged between 8 and 81% [12] However, it has now been well established that at least 21% of PD patients show symptoms of dementia [12-15] Further, there is evidence that PD-related dementia exists in both young- and late -onset patients[4,16]. As noted, estimates of dementia in PD are complicated by other associated factors producing alterations in cognition. The cognitive change is occurring with PD are clinically meaningful whether or not all the criteria for a diagnosis of dementia are fulfilled. Between 20 and 30% of PD patients may have cognitive dysfunction sufficient to impair their daily lives [17]. Studies of PD patients have documented various types of neurocognitive impairment that may be seen with this disorder. Such impairments have included: 1) lower than expected performance IQ scores; 2) slowed thinking (bradyphrenia); 3), visuo-spatial problems; f4) impaired memory, especially on paired associates and list-learning tasks; 5), problems with concept formation, 6) cognitive inflexibility, and 7), reduced semantic fluency [3]. As there is a subcortical component to PD, it is likely that sensitive neurocognitive measures emphasizing speed and efficiency may prove effective measures for the screening of neurological impairment. Some researchers suggest a linkage of PD-related cognitive changes to functions of the basal ganglia's role in planning and modulating ongoing activity via the corticostriatal system [18].

Clinical significance

Routine monitoring of cognition in ad-risk patients with PD is a time-consuming and costly endeavor. Monitoring changes in mood is less time-consuming; however, as noted previously, neurobehavioral changes are frequently missed during routine clinical examination [19]. A traditional neurocognitive examination can take between three and five hours to complete, not counting the room time required to score and tabulate examination results and to generate a clinical report. Whereas the cost of such an examination can very, it can easily range between 600 and $1500 depending upon the time and procedures required. In addition, the availability of this type of examination is dependent on having an appropriately trained neuropsychologist as part of the hospital are clinical staff. As a result of impediments in terms of cost time and availability of staff, and assessment of cognition is frequently not attempted in at-risk patients. Consequently, the availability of tests are automated and efficient in terms of time and cost could prove of great benefit to PD patients. In addition, frequently used neurocognitive instruments have few alternate forms, raising the possibility that previous exposure to the testing material might con found performance. The tests that compose the ANAM battery were specifically designed for repeated assessment, making them ideal for monitoring change and assessing treatment response. Finally, automated procedures such as the ANAM are ideally suited for functional imaging studies in PD. Test items may be presented on a screen and mouse activation requires minimal subject response. Consequently, there is the potential for the same set of measures to be used for screening, monitoring, and research.

Military significance

While it is not known to be chemically-induced, PD affects the dopaminergic system, making it a model for chemical changes that might affect soldiers on the battlefield subsequent to toxic exposure. Specifically, the cognitive changes associated with PD mirror pathology often seen with toxic exposure. Hence, establishing ANAM's sensitivity to cognitive changes found in PD has important implications for the military. The ability to assess disease and exposure in early and potentially preclinical stages has implications for the use of early intervention strategies. ANAM is an automated and portable system developed by the Department of Defense. Data obtained in a Parkinson's study would assist in the validation of the sensitivity to subtle subcortical dysfunction. That might allow the identification of early effects of toxic exposures. Essentially, ANAM could be administered prior to and threw out a soldier's deployment. A model for this type of use already exists. Moreover, a special subset of ANAM has been adopted by the national Aeronautics and space administration to monitor astronauts on the international

space Station. This subset of ANAM is called WinSCAT (space-flight cognitive assessment tool for Windows) [20,21, Kane, Short, Flynn, Christopher]. Operationally, the WinSCAT is administered prior to takeoff in order to establish a pre-mission baseline. It is also part of the astronaut's monthly physical in space. When scat can be administered following any off-nominal of them whose impact under a cognitive functioning needs to be assessed. The potential operational use of ANAM test has also been enhanced by the implementation of ANAM on handheld computers, and by the potential of integrating the system into equipment designed for the soldier of the future. Finally, in addition to the operational uses defined previously, data from the current study can further validate the use of ANAM is a technique for research in the development of agents that may be used as countermeasures for toxic agents.

For the past 25 years, the Department of Defense's been involved in the development of computerized tests to assess and monitor changes in the cognitive status of military personnel [22]. ANAM is the most recent and most technically sophisticated outgrowth of these efforts. The ANAM project began in 1990. The purpose was to adapt a subset of tests developed for neuropsychological assessment and to make them available to clinicians working in medical settings. The driving concept was that ANAM could fulfill a number of emerging needs in clinical medicine. These needs include cost-effective screening and the ability to assess patients and subjects serially over time. Aerial assessment was deemed important for monitoring changes in clinical course and for assessing the effects of pharmaceuticals in both clinical and research settings. In addition, as ANAM grew out of the military performance assessment arena, it was presumed that the development of ANAM for the clinical arena would enhance its utility for military applications. The Department of Defense interesting computerized performance testing is in part related to general concerns regarding chemical and biological Defense. These concerns remain pertinent and a high priority. Hence, there is an obvious relationship between performance monitoring and clinical sensitivity.

ANAM has undergone a steady evolution and expansion since its inception. The present version includes a multilevel set of batteries designed at the upper and to assess fitness for duty in higher functioning patients such as pilots and at the lower and to assess and track patients with progressively dementing conditions. The development has been guided by a continuous series of case studies involving patients from a number of medical center such as the national rehabilitation Hospital, Walter Reed Army medical Center, the national Naval medical Center, and the Baltimore VA medical Center. As a result, ANAM has been "fine-tuned" for clinical use, with modifications guided by patient limitation and examiners need for flexibility in administration and data management. Data analysis support programs now included in the ANAM battery.

Key Research Accomplishments

Objectives of this pilot study were:

1. To validate the use of this brief automated screening battery to assess the presence and severity of cognitive deficits in PD.
2.To further investigate the relationship between the cognitive domains assessed by selected ANAM measures and those assessed by traditional tests used in the assessment of PD patients.
3. To develop a normative base for using selected ANAM measures in PD. By extension, this objective includes an effort to determine normative performance for older individuals.
4. To assess the relationship between a performance on ANAM measures and measures of do the disease severity and functional capacity.

5. To assess the feasibility of using ANAM in an outpatient neurology clinic to assess cognition in PD patients. Issues for investigation include the ability of patients to do the battery and the integration of ANAM into clinical practice.

As will be made clearer in the report of findings, the greatest progress has occurred with regard to objective one. There is strong evidence that the ANAM battery is quite sensitive to cognitive change seen in PD. Progress toward the other goals will increase with the number of assessments completely. As of the date data for this analysis were obtained, the number of patients completing neurocognitive testing has not been sufficient to allow statistical comparison of ANAM measures and traditional neurocognitive measures. Thus objective #2 has not been achieved. While a sufficient number of control subjects have completed ANAM testing to allow the establishment of norm table, the ability to stratify normative data in terms of age and gender awaits an increase in these numbers (Objective #3). While available through another database, functional data will not be explicitly been linked with the present ANAM data until the data are complete (Objective #4). Finally, anecdotal reports from the investigator support the ease of integration of the ANAM battery into an ambulatory neurological clinic. Only two patients with PD have been unwilling to complete the ANAM, in both cases as a result of distress resulting from confirmation of their diagnosis by one of the recruiting neurologists. However, Objective 5 has not been formally evaluated at this time.

A preliminary analysis of the data acquired through August 20, 2005 is presented in the report that follows. At that time, 74 participants with PD and 39 controls completed ANAM testing. Of the PD group, 43 had completed a full neurocognitive evaluation. As the original protocol defined a goal of obtaining 100 controls and 100 patients with Parkinson's disease, recruitment of potential study participants is an ongoing process.

The demographic data for the participant pool appear in Table 1.

Table 1. Demographic Means (sd)

Demograpics		**Age**	**Education**
Female	control (n =24)	63.38 (10.69)	15.2 (3.5)
	pd (n =24)	62.63 (10.57)	14.6 (3)
Male	control (n =13)	60.38 (13.38)	16.08 (2.72)
	pd (n = 48)	62.27 (9.93)	16.48 (2.99)

The ANAM tasks completed by each participant appear in Table 2.

Table 2. ANAM Tasks, Abbreviations and Descriptions

ANAM Task	Abbrev	Task Description
Code Substitution	CDS	Ss determine if a sample pairing a number and symbol is correct by comparing against a reference grid at the top of the screen
Code Substitution Recognition	CDD	Ss are asked to determine if number-symbol pairings from the CDS task is correct after a 20 minute delay
Continuous Processing Task	CPT	Ss determine if a number appearing on the screen is the same or different from the number immediately preceding it in a sequence
Logical Reasoning	LRS	Ss determine whether a statement correctly describe the order of two symbols that follow
Matching to Sample	MSP	Ss view a sample grid then identify which of two grids presented after a brief delay is identical to the sample
Mathematical Processing	MTH	Ss solve simple arithmetic problems and respond by indicating whether the answer is greater or less than 5
Procedural Reaction Time	PRO	Ss respond with to stimulus by determining if it is a low number (2,3) or high number (4,5) with left or right button, respectively
Sternberg Task	STN	Ss learn 6-letter set then determine if individually presented letters were part of the set
Two Choice Reaction Time	CH2	Ss respond as rapidly as possible to stimuli calling for right or left button response

Method for Data Analysis

Data from the ANAM battery were swept into a Microsoft Excel spreadsheet via the Statview program tool from the ANAM Development Team. These spreadsheets were read into a Microsoft Office 2003 Access database. Demographic and neurocognitive test data were entered directly into separate Access databases. After personal identifying information was scrubbed via queries, these data were merged into a comprehensive database and linked to ANAM data via subject numbers.

All analyses were completed with the R Language Version 2.0.1 [23].

Most of the analyses involved testing linear models for which parameters from each ANAM tasks served as dependent variables. Independent variables selected as predictors for observed scores on the dependent variable are explained in later sections.

ANAM accuracy scores are known to present positively skewed distributions that make the use of techniques assuming normal data distribution (parametric statistics) questionable. Individuals taking the ANAM battery tend to correctly answer most items, leading to a clustering of scores near the ceiling of 100% accuracy. Non-parametric techniques requiring no assumptions about the underlying distribution were therefore employed in the analysis of accuracy data.

One caveat to the analytic method is warranted. The data for this study have been collected to assess the feasibility of using ANAM as a tool for detecting subtle cognitive changes in PD; therefore, no attempt was made to control for error inflation due to multiple analyses. That is, although the probability criterion for significance of a single analysis (alpha) is typically accepted to be .05 or lower, the chances that at least one finding might be spurious increases with the number of analyses conducted. An alpha level of .05 is tantamount to accepting a 1 in 20 chance a given analyses might reflect a spurious finding. As the number of analyses increase the cumulative likelihood that one or more of the findings are spurious approaches certainty. Typically, an attempt to minimize this scenario is made through downward adjustments to the acceptable alpha level by means of a correction factor. However, such techniques may result in a lack of power to detect a true effect in smaller samples.

ANAM Parameters Evaluated

The computerized administration allows for the simultaneous acquisition of numerous performance parameters for each ANAM task. This feature is largely unmatched with typical neurocognitive testing for which human administrators must record performance data. ANAM

researchers have typically focused on performance accuracy and response latency (reaction time), two forms of data available during traditional testing but typically not at the same time. A growing body of evidence has indicated that a derivative index of accuracy (Acc) and reaction time (RT) may provide the most effective unit of analysis. This index, known as throughput (TP), quantifies the number of correct responses per unit of working time, thereby providing an estimate of the efficiency of the cognitive process under evaluation.

TPs were chosen to serve as the criterion measure (independent variable) because they have proven sensitive to changes in either of the component parameters. When an analysis of TP scores is found to be significant it is then possible to follow with analyses of RT and Acc to see which elements are responsible for the findings. This method provides a means for not only quantifying how effectively a cognitive process is being performed but also why it might be attenuated by neurological insult. For example, degradation of neural pathways may allow an individual to maintain an accuracy level similar to that of a neurologically-intact person of similar age but only at a cost of longer processing time (i.e. increased response time). Such a change would manifest as a comparatively lower TP score which may be subsequently interpreted in the context of the shift to longer processing time.

Recently, another property of TP scores has been explored for use as a clinical measure by Short and Kane. As TPs represent the efficiency for completion of discrete tasks, it is possible to sum these performance indices across a battery to quantify cognitive achievement in an index of cognitive efficiency (ICE). This final index gives an indication of how accurately and rapidly an individual is able to complete the single ANAM "project" drawing upon various combinations of neurocognitive skills. Because of differences in task complexity and the number of items presented, the Parkinson ANAM components vary in the length of working time necessary for completion. They therefore present substantially different typical throughput scores. The CH2 TP scores are always greatest and would unduly influence any cumulative index if all scores were entered in raw units. Therefore, each task in the ANAM battery must be weighted against the CH2 TP in order to influence the cumulative index equally. Weighting coefficients for the each ANAM task were calculated by taking mean score for the control group and separately dividing each by the mean CH2 TP for controls. The computational definition for weighted ICE (WICE) scores was as follows:

WICE = CH2 TP + (3.7 * CDD TP) + (3 * CDS TP) + (5.2 * LRS TP) + (4.9 * MSP TP) + (5.5 * MTH TP) + (1.2 * PRO TP) + (2.3 * STN TP).

For the WICE calculated for this study, the CPT was omitted. This was because several individuals were not able to master this task. Whereas the CPT demonstrates diagnostic utility as an individual measure, it was decided for the WICE failure to master this single task might possibly bias this comprehensive index.

Neurocognitive Evaluation

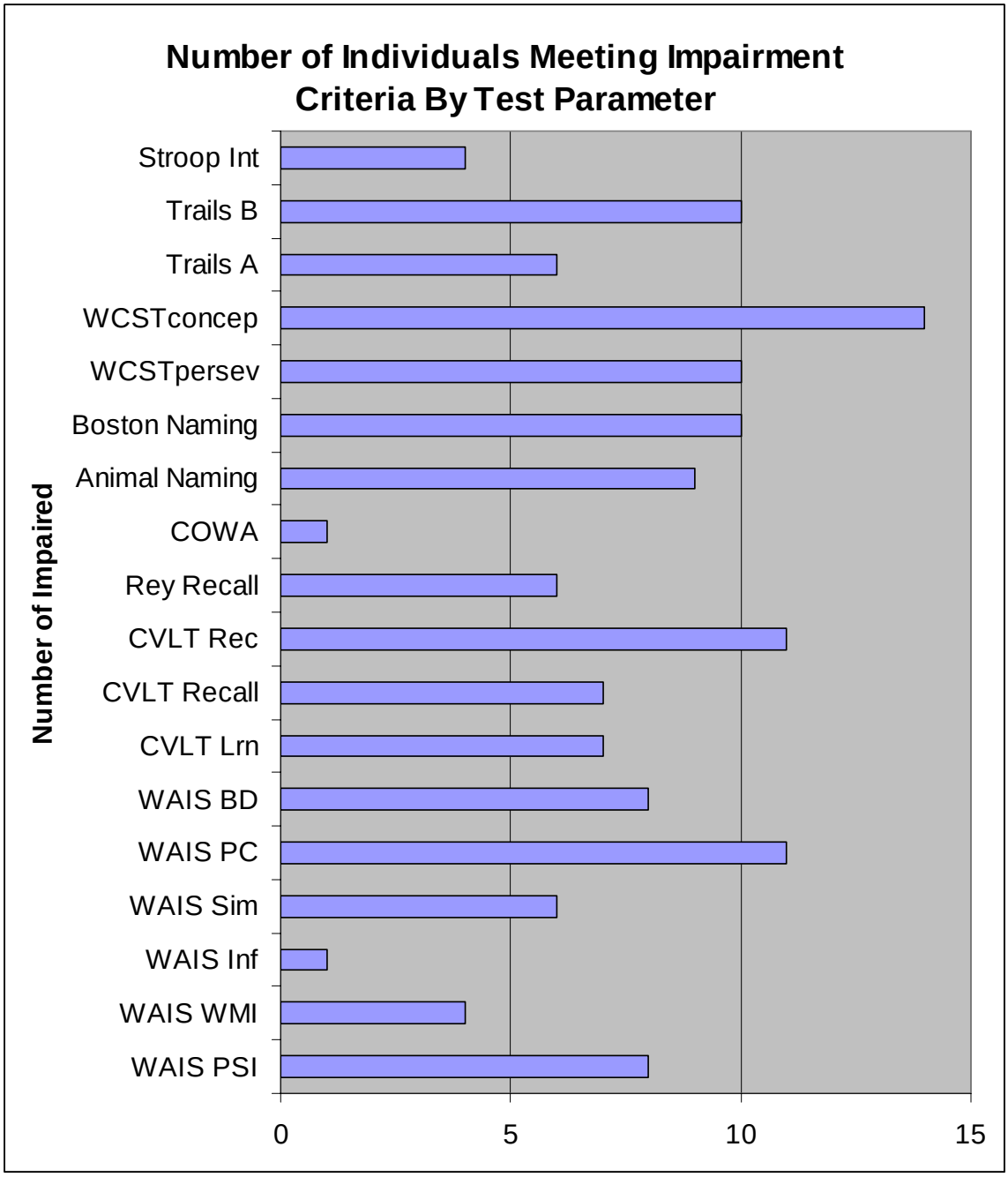
A total of 34 participants had completed a battery of traditional neurocognitive tests at the time of this analysis. These tasks appear in Table 3 with a brief description of the functional domain assessed.

Table 3. Traditional Neurocogntive Tests Indices Included in the Impairment Index

Measure	Functional Domain Assessed
WAIS-III Working Memory Index	Working memory
WAIS-III Processing Speed Index	Processing speed
WAIS-III Block Design	Design analysis and synthesis
WAIS-III Picture Completion	Visual scanning and discrimination
WAIS-III Similarities	Abstract verbal reasoning
California Verbal Learning Test- 2nd Edition Trials Total Score	Verbal acquistion
California Verbal Learning Test- 2nd Edition Long Delay Free Recall	Verbal recall
California Verbal Learning Test- 2nd Edition Discrimination	Verbal recognition
Rey Complex Figure Delayed Recall	Non-verbal recall
Animal Naming	Categorical fluency
Boston Naming Test	Confrontation naming
Wisconsin Card Sorting Test Conceptual Response	Problems solving
Wisconsin Card Sorting Test Perseverative Response	Executive Function
Stroop Word Color Test Interference	Executive Function
Trails A Total Time	Psychomotor Processing speed
Trails B Total Time	Executive Function

Performance on each of these indices was tallied to compute a comprehensive impairment index in the following manner. For any test, performance poorer than one standard deviation below the mean received a score of one. All other were scored as zero. The number of individuals receiving a non-zero score for each task appears in Figure 1.

Figure 1.



Note. Stroop Int = Stroop Word Color Test interference index. Trails B = Trailmaking Test B. Trails A = Trailmaking Test A. WCSTconcep = Wisconsin Card Sorting Test conceptual-level responses. WCSTpersev = Wisconsin Card Sorting Test perseverative responses. COWA = Controlled Oral Word Association Test. Rey recall = Rey Complex Figure Test delayed recall. CVLT Rec = California Verbal Learning Test –II recognition (discrimination). CVLT Recall = California Verbal Learning Test –II delayed recall. CVLT Lrn = California Verbal Learning Test –II recognition learning (trials 1- 5 total). WAIS BD= Wechsler Adult Intelligence Scale III block design. WAIS PC = Wechsler Adult Intelligence Scale III picture completion. WAIS Sim = Wechsler Adult Intelligence Scale III similarities. WAIS Inf = Wechsler Adult Intelligence Scale III information. WAIS WMI = Wechsler Adult Intelligence Scale III working memory index. WAIS PSI = Wechsler Adult Intelligence Scale III processing speed index.

Tests for which all subjects performed within normal limits (e.g. Controlled Oral Word Test) were excluded from further analysis. Based on probability models by Ingraham and Aiken [24] a score of four was used as a cut-point for group membership. This number was chosen because

the likelihood for obtaining at least four scores one standard deviation below the mean for a battery of 16 tests was less than 20%. Thus, 14 participants were designated as impaired (42% of sample), with indexes ranging from 4 to 11. The remaining participants were designated PD normal. Both groups were pooled with control participants for subsequent analysis.

Performance on ANAM parameters are summarized in Table 4 .

Table 4

		PD				PD				PD	
	Control	Normal	Park		Control	Normal	Park		Control	Normal	Park
CH2				**PRO**				**LRS**			
Mean TP	109.81	111.12	76.48	Mean TP	90.47	91.24	71.20	Mean TP	20.94	22.45	12.67
sd	17.61	17.25	19.60	sd	12.94	14.18	16.40	sd	6.67	7.81	8.91
Mean Acc	96.36	94.85	86.79	Mean Acc	91.86	89.65	81.56	Mean Acc	84.28	84.32	57.08
sd	3.81	7.15	14.09	sd	9.26	13.14	8.44	sd	16.95	17.61	15.88
Mean RT	542	527	724	Mean RT	613	595	710	Mean RT	2588	2454	3357
sd	104	112	235	sd	66	86	123	sd	786	795	1101
CDS				**CDD**				**MSP**			
Mean TP	37.12	38.43	24.55	Mean TP	30.91	31.83	21.46	Mean TP	22.65	24.87	15.64
sd	9.00	9.09	9.18	sd	10.87	10.54	7.83	sd	7.12	7.53	7.29
Mean Acc	96.64	96.21	85.79	Mean Acc	85.87	81.67	68.29	Mean Acc	86.34	89.38	74.69
sd	2.97	3.76	14.14	sd	8.95	15.85	15.82	sd	12.94	9.50	14.96
Mean RT	1656	1595	2283	Mean RT	1849	1652	2050	Mean RT	2487	2300	3320
sd	411	428	562	sd	600	386	592	sd	747	552	1243
MTH				**STN**				**CPT**			
Mean TP	20.72	21.32	16.33	Mean TP	47.14	51.57	34.69	Mean TP	75.89	77.33	55.57
sd	5.88	7.04	6.35	sd	12.50	14.86	12.90	sd	14.92	17.14	15.82
Mean Acc	88.61	87.11	81.07	Mean Acc	86.91	87.84	75.46	Mean Acc	86.73	83.97	68.12
sd	14.21	21.56	18.42	sd	14.78	9.27	14.68	sd	11.64	11.51	17.33
Mean RT	2706	2555	3284	Mean RT	1149	1082	1429	Mean RT	742	692	834
sd	558	467	935	sd	249	235	466	sd	125	108	199

Note: Control = Control Group, PD Normal = Non-impaired Parkinson's Disease, Park = Impaired Parkinson Disease

As can be seen in Table 7, the groups differ by age. A one-way analysis of variance (ANOVA) revealed that his difference was statistically significant, $F(2,67) = 5.27$, $p = 0.008$. The group impaired by PD is significantly older than the either of the other two groups. The normal PD group and control group were not significantly different in age, $F(1,53) = 2.46$, $p = 0.12$.

Table 5 Age Mean (sd) by Group

	Control	Park Norm	Park
Age	62.1 (11.7)	57.3 (9.3)	68.8 (7.3)

Note: Control = Control Group, PD Normal = Non-impaired Parkinson's Disease , Park = Impaired Parkinson's Disease

As the three groups differed in age, all analyses included this factor as an independent variable. Hence, a series of linear regression models were tested with group and age predicting throughput scores for a specific ANAM test.

ANAM	F-test	p	Adj R2	PD Group	p	Age	p
CDD	F(3,63) = 6.29	0.0008	0.19	t = -2.18	0.033	t = -2.96	0.004
CDS	F(3,66) = 15.63	< 0.0001	0.39	t = -4.47	< 0.001	t = 10.63	<0.0001
CH2	F(3,61) = 16.02	< 0.0001	0.41	t = 10.56	< 0.0001	t = -2.44	0.018
CPT	F(3,63) = 12.73	< 0.0001	0.35	t = - 3.38	0.0013	t = - 3.95	0.0002
LRS	F(3,66) = 6.62	0.0005	0.20	t = -2.14	0.036	t = -2.85	0.006
MSP	F(3,66) = 14.17	<0.0001	0.36	t = -2.31	0.024	t = -4.80	<0.0001
MTH	F(3,64) = 10.75	0.0036	0.15	t = - 1.63	0.110	t = -2.87	0.006
PRO	F(3,64) = 10.75	< 0.0001	0.30	t = -3.76	0.0004	t = -2.73	0.008
STN	F(3,64) = 7.31	0.0003	0.22	t = -2.46	0.017	t = -2.52	0.014

Table 6 summarizes the results of these 9 analyses. Each of the models was significant. Adjusted R^2 values indicate that age and group membership explain between 15 and 41% of the variance in throughput scores. Age was a significant predictor for all models, whereas membership in the impaired PD group was a significant predictor for all but the MTH task. Although the data do not appear in Table , membership in the unimpaired PD group was not a significant predictor for cognitive efficiency, as each of the p-values for these t-tests exceeded 0.75.

ANAM Accuracy

Two accuracy comparisons were performed. Objective 1 implies that the group determined to be impaired independently of ANAM testing should exhibit meaningful differences from the group previously determined to be cognitively intact. The second comparison evaluated whether similar differences were evident between the unimpaired PD group and controls.

As can be seen in Table 7 , the group showing cognitive impairment was significantly less accurate than the cognitively-intact group. This pattern occurred on seven of eight tests, with only the differences in MTH performance trending toward, but not attaining significance. On the other hand, when the non-impaired PD group was compared with the control group, there were no statistically-meaningful differences in performance. Thus, at least part of the observed difference in cognitive efficiency was due to less accurate processing of the test stimuli by the group showing cognitive change from PD.

The CPT data was not subjected to further analysis because several of the impaired PD patients appeared to perform at a near chance response level. That is, accuracy scores for these individuals were approximately 50%, a level that would be anticipated if an individual randomly pressed a mouse button without considering the stimulus. These findings suggest that the CPT may be difficult for individuals beginning to experience cognitive change. Thus, the CPT likely should be omitted from a final PD ANAM battery if cognitive change is thought to have already occurred.

Table 7. Accuracy for PD Normal vs Impaired and PD Normal v. Controls

Task	Group	Mean Rank	Sum of ranks	Mann-Whitney	Asymp Sig (2 Tail)
CDS	PD Norm	19.31	405.5	35.5	0.003
	Impaired	9.05	90.5		
CH2	PD Norm	17.86	375	66	0.09
	Impaired	12.1	121		
CDD	PD Norm	17.16	326	54	0.06
	Impaired	10.9	109		
LRS	PD Norm	19.71	414	27	0.001
	Impaired	8.2	82		
MTH	PD Norm	17.81	374	67	0.11
	Impaired	12.2	122		
MSP	PD Norm	18.43	387	54	0.03
	Impaired	10.9	109		
STN	PD Norm	18.43	387	54	0.03
	Impaired	10.9	109		
PRO	PD Norm	18.76	394	47	0.01
	Impaired	10.2	102		

Task	Group	Mean Rank	Sum of ranks	Mann-Whitney	Asymp Sig (2 Tail)
CDS	PD Norm	25.9	544	313	0.67
	Control	27.72	887		
CH2	PD Norm	24.19	508	277	0.33
	Control	28.06	870		
CDD	PD Norm	24.71	469.5	279.5	0.63
	Control	26.77	856.5		
LRS	PD Norm	27.95	587	316	0.71
	Control	26.38	844		
MTH	PD Norm	27.95	587	316	0.71
	Control	26.38	844		
MSP	PD Norm	26.93	565.5	334.5	0.98
	Control	27.05	865.5		
STN	PD Norm	23.93	502.5	271	0.24
	Control	29.02	928.5		
PRO	PD Norm	24.81	521	290	0.24
	Control	27.65	857		

Evaluation of WICE scores

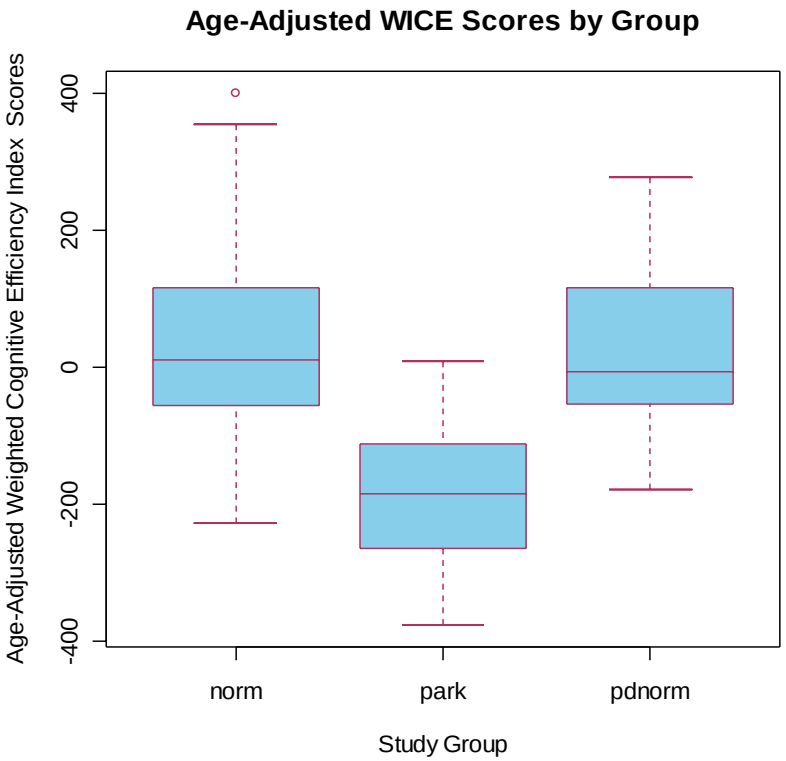
Mean WICE values for each of the study groups appear in Table 8.

Table 8. Weighted Index of Cognitive Efficiency by Study group

	Mean	**SD**
Control	878.97	161.29
PD Normal	906.81	177.08
PD Impaired	598.17	156.25

The differences between groups were tested with a regression model predicting WICE scores and were significant, F(2, 57) = 13.05, p <.0001. Moreover, while membership in the impaired group produced significantly lower scores, t = -4.66, p = .0001, the PD normal group was similar to the control group, t = 0.58, ns. However, as indicated earlier, the groups differed in mean age, with the non-impaired PD group somewhat younger than either of the other groups. When age was controlled for, group membership continued to significantly influence WICE performance, F(2,57) = 10.25, p = .0001. The PD impaired group continued to perform much more poorly, t = -4.38, p = .005. When age was accounted for, group membership explained about 34% of the WICE score variance. As the boxplots in Figure 2 suggest, the PD normal and control groups appear to be virtually indistinguishable, displaying similar levels of median WICE performance.

Figure 2. WICE Performance on Scores Adjusted for Age Effects



Thus, it appears that the WICE scores may provide a reasonable screening method for detecting broad cognitive change in PD patients. One potential use for the new measure is the quantification of efficiency differences among groups. For example, following adjustment for age effects, individuals with impairment demonstrate overall efficiency levels 93% of the control group performance and 89% of the unimpaired PD group. As additional data are acquired for individuals exhibiting impairment on traditional neurocognitive testing, it may become possible to establish WICE cut scores that would allow clinicians to screen PD patients who might require more refined neurocognitive evaluation.

Classification Analysis.

The sensitivity of the WICE scores differences suggest that at a later date, a linear combination of ANAM scores may have predictive value. However, a preliminary logistic regression analysis predicting impairment in patients diagnosed with PD lacked sufficient power in the present sample.

Subsequently, an exploratory discriminant function analysis was performed to examine the weighting of the ANAM tests in the linear combination that best distinguishes groups. The subsequent discriminant function was significant in the present sample, Wilk's lambda = .45, $\chi 2(8) = 18.19$, $p < .02$, producing an Eigenvalue of 1.2. The extracted canonical correlation was .74. The loading of the individual ANAM tasks on the extracted function appear in Table 9 .

Table 9. Loading of ANAM Tasks on Discriminant Function

Test	Loading
CH2TP	0.78
CDSTP	0.74
PROTP	0.64
LRSTP	0.53
STNTP	0.52
MSPTP	0.50
MTHTP	0.46
CDDTP	0.43

The resulting discriminant function correctly classified 83% of the original cases (Table 10). Sensitivity for PD impairment was .80 and specificity was .84. Although discriminant function analyses tend to be unstable with large numbers of predictor variables and a small sample size, the preliminary analysis suggests that the ANAM is likely to have predictive value as a screening test.

Table 10. Classification by Discriminant Function Model

	PD Normal	PD Impaired
PD Normal	16 (84%)	3 (16%)
PD Impaired	2 (20%)	8 (80%)

Conclusions

The findings presented in this report strongly support the utility of the ANAM battery for identifying mild cognitive changes subsequent to PD. What is particularly noteworthy about these preliminary observations is that the ANAM battery was sensitive to impairments identified through traditional neurocognitive testing that would not have otherwise been ordered by the attending physicians. That is, none of the individuals tested would likely have been tapped for follow-up testing of cognition on the basis of the routine clinical examination. In fact, the minimum criterion for selection, a 25 or greater on the MMSE would not normally trigger concerns of incipient dementia. Thus, one of the more immediate uses for ANAM may be as a screening device that allows triage for more extensive confirmatory testing.

When individuals independently identified as presenting with cognitive impairment through traditional neurocognitive testing were considered as a group, the efficiency of their cognitive performance was consistently poorer than both controls and unimpaired PD patients regardless of task. These differences did not appear to be solely the result of age differences between the groups nor could they be attributed to response slowing alone. For all but the MTH test, PD patients showing signs of impairment were clearly significantly less accurate in their level of performance when compared with cognitively-intact PD patients. In fact, the latter did not differ in response accuracy from controls, supporting a hypothesis that there was no qualitative difference between these two groups.

The WICE scores also demonstrated potential clinical utility for identifying individuals experiencing mild cognitive impairment subsequent to Parkinson's disease. This comprehensive index was significantly lower compared with normal controls and Parkinson's patients not experiencing cognitive change. Moreover, this index was sensitive to age- related changes in cognitive performance. When age was controlled for, WICE scores for cognitively-intact Parkinson's patients did not differ from those of normal controls. At the completion of this study, it may be possible to establish cut scores indicating which patients might benefit from more comprehensive evaluation. Building upon the findings with the WICE, it also appears likely that it would also be possible to develop a more precise linear model predicting group membership based on performance on eight tasks. A stable discriminant function model of this type would also prove valuable for identifying individuals likely to be experiencing cognitive decline subsequent to PD. As the pool of individuals receiving a full neurocognitive evaluation approaches 80 - 100 participants, predictive models such as logistic regression analysis and discriminant function analysis should prove more precise.

In terms of overall level of cognitive efficiency, the individuals showing impairment on non-computerized tasks were functioning at an overall efficiency level roughly 10% lower than both controls and cognitively intact PD patients. One theoretical implication for this finding is that cognitive decrements due to PD might manifest as a decline in the net processing resources available for the individual. If cognition is viewed in terms of allotment of a finite resource in a manner that allows the most effective accomplishment of a functional task, degradation of neural pathways might result in impaired functional processing at distinct cerebral loci, slower integration of information arriving from these diverse areas, or both. It is noteworthy that traditional neurocognitive testing failed to evince a specific pattern of functional decline. The most commonly observed deficit was the failure to acquire the conceptual understanding for how to perform a card-sorting task efficiently, a higher-order task that itself models the effective allocation of resources. This finding was followed fairly closely by difficulties with confrontation naming, visual scanning and discrimination of stimuli, and recognition of previously learned verbal stimuli. However, no individual characterized as cognitively impaired exhibited this full spectrum of most common symptoms yet the ANAM closely tracked the

overall pattern of impairment. Thus, declines in cognitive efficiency over a variety of tasks may model the cognitive changes occurring with PD in a more holistic and ecologically valid manner than current approaches viewing cognitive change in terms of changes to discrete functional domains.

ANAM's clinical utility has been informed by a large and growing body of studies articulating its sensitivity to a diverse array of neurocognitive insults, both internal and external [Kane, et al in press]. The characteristics of most of the tests in the battery evaluated in this study, including temporal stability and parallel measure reliability, have been articulated. Thus, in conjunction with the evidence that these select tests are sensitive to cognitive changes resulting from PD, this earlier research supports the use of ANAM as a repeated-measurement instrument for longitudinal studies of cognitive changes over time. ANAM has also proven sensitive to subtle cognitive changes following administration of sedating medications [36, 37, 38], cognitive enhancing medications [39]and countermeasures for fatigue [Kane et al.]. Thus, the present data also support the use of ANAM as an instrument for monitoring cognitive change following drug treatments.

The sensitivity of ANAM to cognitive change with PD also raises the possibility that the instrument might prove valuable as a supplement to the MMSE for screening. Indeed, it is noteworthy that ANAM independently replicated the changes detected by more focused neurocognitive testing; in contrast the MMSE was generally insensitive to these decrements. The battery derived thus far may be administered in as little as 20-25 minutes, suggesting that it might be possible to obtain an estimate of cognitive performance as a routine part of the neurological examination, either through testing in the office or via an Internet interface. ANAM data is currently being acquired in the latter manner as part of a longitudinal telemedicine study of multiple sclerosis at the VA Multiple Sclerosis Center of Excellence East at the Baltimore facility.

Finally, because ANAM is mouse-activated, the minimal motion during testing makes it ideal for imaging studies. The demonstrated sensitivity to PD-related cognitive decline suggests that PD researchers would be justified in exploring several of the individual tests for imaging studies.

Although the present results are encouraging and supportive of the aforementioned projects, work on the remaining objectives is critical. Of particular importance is the need to develop norms for men and women older than age 40, the typical upper limit for military-based studies of ANAM. Such norms will allow the extension of ANAM into a number of clinical milieus. Thus, focus on testing of spouses remains one highly desirable goal.

References

1. Hernandez, L.M., et al., eds. *Gulf War Veterans: Measuring Health, Division of Health Promotion and Disease Prevention, Institute of Medicine*. 1999, National Academy Press: Washington, DC.
2. Reeves, D., et al., *Automated Neuropsychological Assessment Metrics (ANAM V3.11): Clinical and neurotoxicology subsets*. 1995, National Cognitive Recovery Foundation: San Diego.
3. Soukup, V.M. and R.L. Adams, *Parkinson's Disease*, in *Neuropsychology for Clinical Practice: Etiology, Assessment, and Treatment of Common Neurological Disorders*, R.L. Adams, et al., Editors. 1996, American Psychological Association: Washington, DC. p. 243-267.
4. Schrag, A., et al., *Young-onset Parkinson's disease revisited--clinical features, natural history, and mortality.* Mov Disord, 1998. **13**(6): p. 885-94.
5. American Parkinson's Disease Association, 1995.
6. Parkinson, J., *An essay on the shaking palsy*. 1817, London: Sherwood, Neely, & Jones.
7. Anderson, K.E. and W.J. Weiner, *Psychiatric symptoms in Parkinson's disease.* Curr Neurol Neurosci Rep, 2002. **2**(4): p. 303-9.
8. Marsh, L., *Neuropsychiatric aspects of Parkinson's disease.* Psychosomatics, 2000. **41**(1): p. 15-23.
9. Shulman, L.M., et al., *Comorbidity of the nonmotor symptoms of Parkinson's disease.* Mov Disord, 2001. **16**(3): p. 507-10.
10. Folstein, M.F., S.E. Folstein, and P.R. McHugh, *"Mini-Mental State": a practical method for grading the mental state of patients for the clinician.* Journal of Psychiatric Residency, 1975. **12**: p. 189-198.
11. Rothlind, J.C. and J. Brandt, *A brief assessment of frontal and subcortical functions in dementia.* J Neuropsychiatry Clin Neurosci, 1993. **5**(1): p. 73-7.
12. Aarsland, D., et al., *Frequency of dementia in Parkinson disease.* Arch Neurol, 1996. **53**(6): p. 538-42.
13. Bayles, K.A., et al., *Change in cognitive function in idiopathic Parkinson disease.* Arch Neurol, 1996. **53**(11): p. 1140-6.
14. Lees, A.J., *Parkinson's disease and dementia.* Lancet, 1985. **1**: p. 43-44.
15. Taylor, A., J.A. Saint-Cyr, and A.E. Lang, *Dementia prevalance in Parkinson's disease.* Lancet, 1985. **1**: p. 1037.
16. Mayeux, R., et al., *A population-based investigation of Parkinson's disease with and without dementia: Relationship to age and gender*. Archives of Neurology, 1992. **49**: p. 492-497.
17. Mayeux, R. and Y. Stern, *Intellectual dysfunction and dementia in Parkinson's disease*, in *The Dementias*, R. Mayeux and W.G. Rosen, Editors. 1983, Raven Press: New York. p. 211-227.
18. Gabrieli, J.D.E., *Contributions of the basal ganglia to skill learning and working memory in humans*, in *Models of Information Processing in the Basal Ganglia*, J.C. Houk, J.L. Davis, and D.G. Beiser, Editors. 1994, MIT Press: Cambridge, MA. p. 277-294.
19. Shulman, L.M., et al., *Non-recognition of depression and other non-motor symptoms in Parkinson's disease.* Parkinsonism Relat Disord, 2002. **8**(3): p. 193-7.
20. Flynn, C., et al. *Background and Development of the Space Flight Cognitive Assessment Tool*. in *71st Scientific Meeting of the Aerospace Medical Association*. 2000. Houston.
21. Kane, RL, Short, P, Sipes, W., & Flynn, CW. (in press). Development and validation of the Space-flight Cognitive Assessment Tool for Windows (WinSCAT). Aviation, Space, & Environmental Medicine.
22. Kane, R.L. and G.G. Kay, *Computerized assessment in neuropsychology: A review of tests and test batteries.* Neuropsychology Review, 1992. **3**(1): p. 1-117.

23. R Core Development Team, 2004. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org.
24. Ingraham, L J & Aiken, CB.1996. An empirical approach to determining criteria for abnormality in test batteries with multiple measures. Neuropsychology, 10, 120-124.